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I. Remarks

Claims 1-16, 18-34, 36-49, and 51-52 are currently pending.

Claims 17, 35, and 50 have been canceled with this response.

Claims 1, 2, 5, 6, 10-16, 19, 20, 23, 24, 28-34, 36-39, and 43-49 have been amended with this response. Claims 5-16, 23-34, and 38-49 have been amended with this response in order to rewrite each in independent form including all of the limitations of the base claim and any intervening claims. Accordingly, Applicants do not believe that these amendments have added new matter. Claims 1, 2, 19, 20, 36, and 37 have been amended with this response to clarify that, upon cleavage by the appropriate enzyme, two peptides are released comprising Factor VII heavy chain and Factor VII light chain molecules. Support for this amendment is found in the instant specification and particularly at page 10, lines 25-30, for example. Accordingly, Applicants do not believe that these amendments have added new matter. Applicants therefore respectfully request the entry of the amendments set forth herein.

Applicants thank the Office for indicating that claims 5-16, 23-34, and 38-49 represent allowable subject matter.

Applicants also thank the Office for indicating the withdrawal of the rejection of claims 2, 4, 17-18, 20, 22, 35, 37, 50, and 52 under 35 U.S.C. § 112, first paragraph.

II. Claim rejections under 35 U.S.C. § 112

Claims 17, 35, and 50 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in such a way as to enable the skilled artisan to make and/or use the instant invention. In particular, the Office has concluded that it would have required undue experimentation to practice the instantly claimed invention because the SKI-1 consensus sequence as taught in the art at the time of the invention and SEQ ID NO. 9 are not the same.

In the interest of furthering prosecution and without acceding to the correctness of the instant rejection, claims 17, 35, and 50 have been canceled. Accordingly, this rejection is moot. Its withdrawal is respectfully requested.

III. Claim rejections under 35 U.S.C. § 102(e)

Claims 1, 3, 18-19, 21, 36, and 51 stand rejected as allegedly being anticipated by WO 01/70763 (High et al., 2001), which designated the U.S. and was published in English and claims priority to U.S. Provisional application no. 60/191,331 filed on March 22, 2000. Specifically, the Office has concluded that the cited art anticipates the instant claims by teaching the insertion of the furin cleavage site between amino acids 152-153 of Factor VII. Applicants respectfully traverse.

The 60/191,331 application cannot anticipate the instant claims because the methods taught therein utilize different DNA vectors from those of the instant claims and the polypeptides produced by the 60/191,331 methods are different from those of the instant claims as well. In particular, the instant claims as amended specify that the intracellular cleavage of the polypeptide results in the generation of only two peptides- one comprising a Factor VII heavy chain and one comprising a Factor VII light chain.

As argued earlier in the prosecution of this case, the disclosure of the 60/191,331 application does not and cannot anticipate the instant claims. In the particular embodiment claimed herein, Applicants utilize modified Factor VII polypeptides capable of conversion to activated Factor VII when expressed in an individual. The endogenous Factor VII activation cleavage sequence is mutated to encode for a non-endogenous enzymatic cleavage site capable of being cleaved when expressed intracellularly (see the instant specification at page 6, lines 27-29.) Intracellular cleavage of this polypeptide results in the generation of only two peptides- a Factor VII heavy chain and a Factor VII light chain.

In contrast, the 60/191,331 teaches the insertion of additional amino acid sequences that code for an enzymatic cleavage site into the human Factor VII sequence rather than mutation of the endogenous sequence. By utilizing insertion, intracellular cleavage of the 60/191,331 polypeptide results in the generation of three peptides comprising: 1) a small peptide comprising some portion of the inserted sequence, 2) a Factor VII heavy chain, and 3) a Factor VII light chain.

The passage cited by the Office as anticipatory from the 60/191,331 application, which relates to protease cleavage sites for use in an engineered FVII, is located on page 2, in the first full paragraph reproduced below.

> "The invention proposes the use of an engineered factor VII such that upon synthesis and secretion from the cell, it is released as active factor VII such that upon synthesis and secretion from the cell, it is released as active factor VII (FVIIa). In order to accomplish this a protease cleavage site (such as, but not limited to, a PACE/furin site) will be inserted at the normal site of activation (between amino acids Arg^{152} - Ile^{153}). Thus, upon synthesis of the engineered factor VII in the endoplasmic reticulum and Golgi apparatus, the protease recognizing the inserted

cleavage site will proteolyze the engineered factor VII releasing a small peptide and generating two chain activated factor VII (FVIIa) which is then released into circulation."

The language of this passage unequivocally states that "...a protease cleavage site (such as, but not limited to, a PACE/furin site) will be inserted at the normal site of activation (between amino acids Arg^{152} - Ile^{153})." Furthermore, the passage contemplates that a small peptide and two chains will be released upon cleavage of the construct. It does not give alternative means to accomplish the generation of an engineered factor VII nor would the skilled artisan read the passage to suggest that alternates are part of the invention. Figure 1 of the 60/191,331 application provides the same disclosure. This flow diagram shows that the cleavage site is inserted into the FVII molecule to produce an engineered FVII. Intracellular processing of the construct leads to generation of activated FVII and removal of the protease cleavage site.

Therefore, the 60/191,331 application cannot anticipate the instant claims because the methods taught therein utilize different DNA vectors from those of the instant claims and the polypeptides produced by the 60/191,331 methods are different from those of the instant claims as well. Accordingly, Applicants respectfully request that this rejection be withdrawn.

IV. Claim rejections under 35 U.S.C. § 103(a)

Claims 2, 4, 20, 22, and 37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 01/70763 (High et al., 2001), in view of Seidah et al. (1999) Brain Research, vol. 848, 45-62. In particular, the Office has concluded that it would have been obvious to one of ordinary skill in the art to substitute the SKI-1 cleavage site provided by Seidah et al. for the furin site in the High et al. vectors, in light of the motivation provided by High et al. to modify FVII. Applicants respectfully traverse because the Office has not established a *prima facie* case of obviousness.

The establishment of this *prima facie* case requires three basic criteria. MPEP 2142-2143 outlines these criteria, which the Federal Circuit has consistently required in establishing obviousness where references are combined. There 1) must be a teaching, motivation, or suggestion shown by the Office to combine the cited references; 2) all claim limitations must be taught or suggested by the references; and 3) there must be a reasonable expectation of success in making the combination of the references. All claim limitations required to arrive at the instant invention are not taught or suggested by the references cited by the Office. In addition, the Office has not provided a teaching, motivation, or suggestion to combine the cited references. Thus, a *prima facie* case of obviousness cannot be established by the instant combination of the references.

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As discussed supra, only the subject matter present in the 60/191,331 application, filed March 22, 2000, can properly be considered prior art against the instant claims. The application teaches the insertion of additional amino acid sequences that code for an enzymatic cleavage site into the human Factor VII sequence rather than mutation of the endogenous sequence. As such, intracellular cleavage of the 60/191,331 polypeptide results in the generation of three peptides: 1) a small peptide comprising some portion of the inserted sequence, 2) a Factor VII heavy chain, and 3) a Factor VII light chain. In contrast, the instant claims are directed to a methods and compositions wherein intracellular cleavage of the Factor VII polypeptide results in the generation of only a Factor VII heavy chain and a Factor VII light chain. Therefore, all claim limitations are not taught or suggested by the cited references.

In addition, the passage cited by the Office from WO 01/70763 as providing motivation to combine WO 01/70763 with Seidah et al. is not present in the 60/191,331 application. Accordingly, the Office has not provided a motivation to combine the cited references to arrive at the instant invention.

Absent a teaching or suggestion of all claim limitations in the cited references and absent a motivation to combine, a prima facie case of obviousness has not been established. As such, Applicants respectfully request withdrawal of the instant rejection.